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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,853	07/26/2001	Takafumi Ueno	12013/58002	7372

26646 7590 11/06/2002

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EXAMINER

YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 11/06/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/915,853

Applicant(s)

UENO ET AL.

Examiner

Christopher H Yaen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-69 is/are pending in the application.
- 4a) Of the above claim(s) 4, 17, 26, 35, 50-52 and 56-69 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in Paper No. 7 is acknowledged. Applicant has also selected heart muscle as the elected species.
2. Claims 1-64 are pending in the instant application, claims 4,17,26,35,50-52, and 56-64 are withdrawn from consideration as being drawn from a non-elected subject matter. Claims 1-3, 5-16, 18-25, 27-34, 36-49, and 53-55 are examined on the merits.

Information Disclosure Statement

3. The Information Disclosure Statement filed 9/23/02 (paper no. 7) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. Claims 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Regarding claim 44 in the recitation of the term "regenerating", it is unclear as to whether the regeneration is referring to the re-manufacturing of tissue *de novo* or the repair of tissue. As such, the metes and bounds of the term cannot be adequately established. For the purposes of examination, the term "regenerating" will be interpreted as meaning repair.

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6. Regarding claims 1, 12, 23, 32, 39, 44, and dependent claims thereof, in the recitation of the term “effective”, it is indefinite and unclear because one of skill in the art would not be able to understand the metes and bounds of the term, because the actual amount that is effective may vary according to the subject to which the method is practiced.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1-3, 5-16, 18-25, 27-34, 36-49, and 53-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, “The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...”. The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring “ingenuity beyond that to be expected of one of ordinary skill in the art” (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement

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requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are drawn to a methods of forming new blood vessels, increasing blood flow, treating disease, increasing angiogenesis, preventing heart failure, and regenerating tissue through the administration of bone marrow mononuclear cells (BM-MNC), wherein the administration of BM-MNC is intended to re-vascularize ischemic cardiac tissue through the formation of capillaries or collateral vessels.

The state of the prior art and the predictability or lack thereof in the art: The art teaches bone marrow cells (BMC) contain many types of cells of which are non-differentiated. BMCs will eventually give rise to differentiated cells such as endothelial cells, which are the cells that make up the blood vessels. The differentiation of BMCs into endothelial cells is accomplished through the stimulation of endothelial progenitor cells (EPC) (a cell type found in the BMC) by cytokines and growth factors such as VEGF (see Hamano *et al* Surgery 2001 July; 130(1):44-54, Applicant IDS). Once the EPCs are differentiated into endothelial cells, blood vessels will form.

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The nature of the instant invention is drawn to the formation of blood vessel from BM-MNC, a sub-fraction separated from the general pool of BMC. Found within this fraction are EPC, which are the cell of interest and the cells which are required to make endothelial cells. As stated in the specification (page 21 lines 1-5) and in the art (Prockop D Science 1997; 276:71-74) the BM-MNC contain other types of cells, which may not be necessary for the formation of blood vessels. The disclosure of the instant specification has not adequately described the steps which are necessary to perform the instant invention, because the claims are directed to the administration of a general pool of BM-MNC, ^{while} will the cell type required for the invention, namely the EPCs, is not taught. As stated earlier, the addition of cytokines and growth factors, such as VEGF, are required for the differentiation of EPCs into endothelial cells, of which no mention is made in the claims or in the specification. Is one of skill in the art to presume that such growth factors are going to be present in the area to which the BM-MNC are to be administered? The claims are drawn to the simple administration of BM-MNC, with no recitation of additional growth factors or cytokines. Further, in order for the invention to work, EPCs must be present within the BM-MNC fraction of BMCs. Lastly, since BM-MNC contain additional cells types, how can one of skill in the art be certain that the practice of the instant invention may not be deleterious to the subject. The dosages and side effects of BM-MNC addition are not known. As such, one of skill would not know given the knowledge of the present art whether the administration of BM-MNC would adequately function in the manner described, because of cytokine/growth factor requirements, the presence of an adequate amount of EPCs within the BM-MNC

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fraction, and the effects of the other cell types on the administration of BM-MNC to a specific site, are not known.

The breadth of the claims and the quantity of experimentation needed: Given the numerous factors that may effect the outcome of the invention, in terms of functionality, and given the uncertainty of certain aspects of the invention, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1-8, 10, 12-13, 15-16, 18-21, 23-28, 30, 32-34, 36-37, 39-40, 42, 44-45, 47-49, and 53-54 are rejected under 35 U.S.C. 102(a) as being anticipated by Kobayashi *et al* (J. Surgical Res. 2000 Apr; 89(2):189-95). Claims are drawn to methods of forming new blood vessels, increasing blood flow, treating disease, increasing angiogenesis, preventing heart failure, and regenerating tissue through the administration of bone marrow mononuclear cells (BM-MNC), wherein the administration of BM-MNC is intended to re-vascularize ischemic cardiac tissue that is artificially created in mammals through the formation of capillaries. Kobayashi *et al* teach the administration of self BM-MNC to a mammal wherein the mammal is artificially induced to have an ischemic area in the heart through the ligation of the left anterior

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descending artery with a suture. The administration of self BM-MNC, as taught by Kobayashi *et al*, enhances the angiogenesis to the damaged area through the formation of microvessels. Inherently, the administration of BM-MNC to the animal will increase blood flow, treat disease, prevent heart failure, and repair/regenerate damaged tissue.

10. Claims 1-2, 5-8, 10-15, 18-21, 23-24, 27-30, 32-33, 36-37, 44-48, and 53-54 are rejected under 35 U.S.C 102 (a) as being anticipated by Shintani *et al* (Circulation 1999 Nov 2; 100(18):1406, Abstract, Applicant IDS). Claims are drawn to methods of forming new blood vessels, increasing blood flow, treating disease, increasing angiogenesis, and regenerating tissue through the administration of bone marrow mononuclear cells (BM-MNC), wherein the administration of BM-MNC is intended to re-vascularize ischemic tissue that is artificially created in mammals through the formation of capillaries and or collaterals. Shintani *et al* teach the administration of autologous BM-MNC to an ischemic hind limb of a rabbit, wherein the administration of the BM-MNC to the artificially created ischemic area increased the blood flow through the formation of collateral blood vessels and hence angiogenesis.

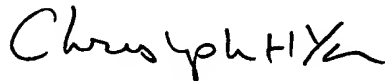
Conclusion

No claim is allowed

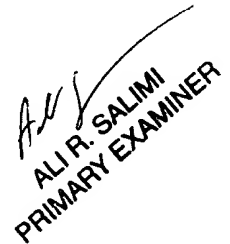
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Christopher Yaen
Art Unit 1642
October 31, 2002



ALI R. SALIMI
PRIMARY EXAMINER